

Long-Term Prognosis of Patients With Anginalike Chest Pain and Normal Coronary Angiographic Findings

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Objectives. This study analyzes the long-term course of patients with typical angina pectoris or anginalike chest pain and normal coronary angiographic findings.

Background. In previous studies of such patients the rate of occurrence of typical coronary events during follow-up has differed widely, depending on the duration of the study and the number of patients.

Methods. One hundred seventy-six patients (mean age 48.3 years) who underwent coronary and left ventricular angiography for typical angina or anginalike chest pain were followed up for 5.8 to 15.8 years (median 12.4). By definition, all patients had normal findings on coronary and left ventricular angiograms; exercise test results were positive in 31.

Results. Fourteen patients (8%) had a coronary event (0.65%/year) after an average of 9.3 years (median 9.2). Two of the 14 died of a coronary event (0.09%/year), 1 of cardiogenic shock during acute myocardial infarction, 1 suddenly; 4 had a nonfatal myocardial infarction at an average of 8.1 years (median 9.1); 8 had

severe angina pectoris after an average of 10.3 years (median 11.1), confirmed by a second angiogram, now with positive findings. Two patients died of a noncoronary cardiac event (chronic cor pulmonale due to obstructive lung disease, acute pulmonary embolism), eight of a noncardiac cause, mainly cancer. None of the 31 patients with a positive exercise test result had a coronary event. Patients with a coronary event had significantly more risk factors (hypercholesterolemia, hypertension, cigarette smoking, diabetes type II) than did those without an event (average 2.4/patient vs. 1.3/patient, $p < 0.01$). Chest pain persisted in 133 (81%) of the 164 survivors and disappeared in 31 (19%).

Conclusions. Patients with typical angina or anginalike chest pain and normal coronary angiograms have a good long-term prognosis despite persistence of pain for many years; coronary morbidity and mortality are similar to those of the overall population. An increased risk for the development of coronary events is present mainly in patients with elevated risk factors.

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Patients with typical angina pectoris or anginalike chest pain but normal coronary angiographic findings despite positive exercise test results are frequently seen (1-17). However, little is known about their long-term prognosis, and the few studies available (9,12,17) are contradictory with regard to the incidence of coronary events during follow-up. The discrepancy is mainly due to the small number of patients, often <100 (2,11,17), and the short follow-up period, often <5 years (8,13,15). However, an increasing number of patients with anginalike chest pain and inconclusive noninvasive tests for ischemia undergo coronary angiography, which has become a technique of low risk with a relatively high sensitivity for diagnosing clinically relevant coronary artery disease (18). To obtain a more precise prognosis, we followed up a large number of such patients for 5.8 to 15.8 years (median 12.4). End points were fatal or nonfatal myocardial infarction, sudden coronary death and typical angina confirmed by positive coronary angiographic findings.

Methods

Patients (Table 1). The study includes 176 patients (61 women, 115 men with an average age of 48.3 years [range 21 to 68]) with chest pain typical or suggestive of angina pectoris. They underwent coronary angiography between January 1, 1978 and August 31, 1985, a period in which 7,670 patients had diagnostic coronary angiograms in our institution. By definition, all patients had normal coronary and left ventricular angiographic findings (18). We excluded patients with abnormal coronary angiographic findings, even those with minimal isolated lesions or wall irregularities, and patients with normal coronary angiographic findings who had cardiomyopathy or congenital, rheumatic or valvular disease.

Symptoms and signs. By definition, all 176 patients had symptoms typical or suggestive of angina (anginalike chest pain) (Table 1); in addition, 79 of the 176 had dyspnea during exertion and 27 had episodes of palpitation.

Typical angina pectoris was defined as exercise-induced pain in typical locations (retrosternal, left shoulder, left arm) prevented or interrupted by nitroglycerin (for definition see also Ref. 1 to 3). The definition of *anginalike chest pain* included abnormal pain location (i.e., in the right side of the chest or right arm), atypical pain characteristics like stabbing or burning and pain of long duration (>1 h), independent of exercise,

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Table 1. Clinical Characteristics of 176 Patients at Initial Coronary Angiography and 164 Survivors at Follow-Up

	Initial		Follow-Up*	
	No.	%	No.	%
Patients	176	100	164	100
Age (yr)				
Mean	48.3			
Range	21 to 68			
Gender				
Female	61	34.7	58	35.4
Male	115	65.3	106	64.6
Symptoms				
Typical angina	31	17.6	15	9.1
Anginalike chest pain	145	82.4	118	72.0
Free of symptoms	0	0	31	18.9
Rest ECG†				
Normal	87	49.4		
Nonspecific ST-T wave changes	51	29.0		
Left ventricular hypertrophy	4	2.3		
Right bundle branch block	3	1.7		
Compatible with infarction	39	22.2		
Exercise ECG				
Positive (ST ↓ ≥0.1 mV)	31	17.6		
Negative at max. heart rate	75	42.6		
Prematurely interrupted	48	27.3		
Not performed	22	12.5		
Medication‡				
Nitrates	123	69.9	38	23.2
Beta-adrenergic blocking agents	65	36.9	21	12.8
Calcium channel blocking agents	43	24.4	56	34.1
Digitalis	30	17.0	14	8.5
No medication	19	10.8	34	18.9
Diuretic drugs	17	9.7	27	16.5
Aspirin or anticoagulant agents	8	4.5	28	17.1

*Data based on 164 survivors. †Data add to >176 because some patients had >1 ECG alteration or >1 medication, or both. ECG = electrocardiogram; max. = maximal; ST ↓ = ST segment depression.

and not always relieved by nitroglycerin. Eleven patients presented these symptoms for the first time and underwent angiography to exclude unstable angina. Typical angina was present in 31 patients (18%), anginalike chest pain in 145 (82%).

Rest electrocardiograms (ECGs) showed normal findings in only 87 patients (49%); the others showed various abnormalities, but only patients with left bundle branch block were excluded (Table 1). In 39 patients the ECG was compatible with old myocardial infarction (abnormal Q waves or loss of R waves); however, none of the 39 had a history of infarction or abnormal findings on left ventricular angiography (i.e., abnormally contracting areas).

Exercise tests using a modified Bruce protocol were performed in 154 patients (87.5%); results were positive in 31 patients (20% of tests) (ST segment depression ≥0.1 mV) and negative in 75 (49% of tests) although maximal heart rate was achieved; results in 48 patients (31%) were classified as inconclusive because of insufficient heart rate increase, hypertension or premature interruption due to severe chest pain; 22

patients did not undergo exercise testing because of contraindications (left bundle branch block, abnormal ST segments at rest).

Antianginal drug treatment (Table 1). At the time of angiography, 157 patients (89%) had been receiving prophylactic antianginal treatment for several months; the majority were receiving long-acting nitrates (123 patients), beta-adrenergic blocking agents (65 patients) or calcium antagonists (43 patients); a minority had been taking digitalis, diuretics, aspirin or anticoagulant agents.

Risk factors. Risk factors were defined as total cholesterol ≥6.7 mmol/liter, hypertension (systolic pressure >160 mm Hg, diastolic >90 mm Hg), smoking ≥10 cigarettes/day and diabetes mellitus type II. Thirty-three patients were without these risk factors for coronary artery disease, 73 had one risk factor and 70 had two or more.

Angiography. Cardiac catheterization included left ventricular and coronary angiography in two planes (60° left anterior oblique, 30° right anterior oblique), performed by the Judkins or Sones technique. Before angiography, nitroglycerin, 0.8 mg sublingually, was administered to achieve maximal coronary artery dilation (19). Coronary angiograms were performed in several standard and half-axial projections, usually including a total of 10 to 12 scenes. All coronary angiograms were analyzed by two experienced independent investigators. Only angiograms with visually smooth contours without any wall irregularities were accepted as normal. All patients showed a normal left ventricle with normal contraction; left ventricular ejection fraction, calculated by the area-length technique from systolic and end-diastolic left ventricular contours obtained in the right anterior oblique projection, averaged $66.8 \pm 7.2\%$ and was >55% in all patients. Provocative tests for coronary artery spasm were not performed.

Follow-up. The follow-up period ended in November 30, 1993, after a median interval of 148.5 months (range 70 to 190, i.e., a maximum of 15.8 years). Of the 176 patients, 93 (53%) had been followed up for >12 years, 38 (22%) for <10 years.

Most patients were followed up in the outpatient clinic at the Hannover Medical School; in addition, all received questionnaires concerning their symptoms, the occurrence of new events (myocardial infarction, severe arrhythmias, heart failure), subsequent cardiovascular examinations, changes in cardiac medication, hospital admissions elsewhere and coronary angiograms repeated in other institutions. In addition, family physicians were questioned by telephone, especially about death or nonfatal myocardial infarctions.

Statistics. Results were analyzed by paired and unpaired *t* tests, chi-square tests and Wilcoxon tests; median values were calculated for follow-up duration. A *p* value < 0.05 was accepted as significant.

Results

Clinical course of patients (Table 1). At the end of the follow-up period, 164 patients (93%) had survived; however, only 31 (19% of survivors) were free of symptoms. One

Table 2. Characteristics of the 12 Patients Who Died

Pt No.	Age (yr)*/Gender	Total Cholesterol* (mmol/liter)	Months of FU	Cause of Death	
				General	Specific
1	57/M	7.3	78	Coronary	Sudden coronary death
2	60/F	6.2	93	Coronary	Acute myocardial infarction, cardiogenic shock
3	60/M	5.7	70	Cardiac	Cor pulmonale, chronic obstructive lung disease
4	54/F	5.9	93	Cardiac	Pulmonary embolism from deep leg vein thrombosis
5	53/M	6.6	87	Cerebral	Intracerebral bleeding, stroke
6	71/F	5.8	147	Cerebral	Central apnea, stroke
7	59/M	5.2	99	Carcinoma	Colonic tumor
8	67/F	5.5	111	Carcinoma	Gastric tumor
9	64/M	6.3	119	Carcinoma	Colonic tumor
10	65/M	6.5	146	Carcinoma	Ureteral tumor
11	60/M	6.0	168	Carcinoma	Prostatic tumor
12	62/M	6.3	124	Other	Suicide

*At study entry. F = female; FU = follow-up; M = male; Pt = patient.

hundred thirty-three patients (81% of survivors) still reported chest pain (Table 1), although its character had changed in some. Typical angina pectoris was still present in 15 of the initial 31 patients (48%) and anginalike chest pain in 118 (81% of the initial 145); in 63 patients the pain was unchanged, in 55 it had lessened and in 15 it had become worse. Forty-four patients had been admitted to the hospital once or several times for chest pain, including the 14 patients who had a coronary event (Tables 2 and 3).

Exercise electrocardiograms. None of the 31 patients with initially positive exercise test results had a coronary event during the follow-up period; however, 2 of them died, 1 of pulmonary embolism (Table 2, Patient 4) and 1 by suicide (Patient 12).

Mortality (Table 2). Twelve patients died during follow-up, four from cardiac causes, including two who died of coronary artery disease. One of the latter two (Patient 1) was found dead 78 months after coronary angiography; because of several risk factors (total cholesterol 7.3 mmol/liter, blood pressure averaging 160/100 mm Hg, heavy nicotine abuse), ECG signs compatible with an old posterior wall infarction and anginalike chest pain present throughout follow-up, sudden coronary death was accepted as the most plausible cause. The other (Patient 2) died 93 months after coronary angiography of

cardiogenic shock due to an extended anterior wall infarction. The other two cardiac deaths were of noncoronary origin (one in a patient with cor pulmonale due to chronic obstructive lung disease and one due to acute pulmonary embolism). Eight other patients died of a noncardiac cause, including five with cancer. No autopsies were performed; the diagnoses were based entirely on clinical data received from other hospitals, attending physicians and family members. The total mortality rate was 6.8% (0.55%/year), cardiac mortality rate 2.3% and coronary mortality rate 1.14% (0.09%/year); the latter rate was not higher than that in the overall population (20).

Nonfatal myocardial infarctions (Table 3). The four nonfatal infarctions occurred 33 to 140 months after initial angiography; all four patients underwent a second coronary and left ventricular angiographic study that demonstrated single-vessel disease and an anterior wall infarct in one patient and a posterior wall infarct in three. All four patients, at the time of the first angiogram, had normal cholesterol levels (average 6.08 mmol/liter); however, three were hypertensive, two had diabetes type II and three were cigarette smokers.

Other coronary events. Forty-three patients (24%) were admitted to the hospital one or several times for pain suggestive of angina. As a result, 21 of the 43 underwent a second coronary angiogram after a median period of 113.5 months

Table 3. Characteristics of the Four Patients With Nonfatal Myocardial Infarction

Pt. No.	Age (yr)*/ Gender	Months of FU	Risk Factors	Total Cholesterol at Study Entry (mmol/liter)	Infarct site; Angiographic Data; Treatment
13	52/M	33	Hypertension, diabetes type II	6.0	Anterior wall MI; angiogram, LAD 75% stenosis; thrombolysis
14	49/M	107	Hypertension, hypertriglyceridemia, smoking	6.3	Inferior wall MI; angiogram, RCA 90% stenosis; thrombolysis, PTCA
15	46/M	111	Hypertension, hypertriglyceridemia, smoking	5.8	Inferior wall MI; angiogram, RCA 100%; medical treatment only
16	55/M	140	Smoking, diabetes type II	6.1	Inferior wall MI ~1 year after PTCA of LAD; no 3rd angiogram; medical treatment only

*At study entry. LAD = left anterior descending coronary artery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; other abbreviations as in Table 2.

(range 13 to 177). The repeat study demonstrated coronary disease in 12 patients, including the four patients with a nonfatal myocardial infarction; the other eight patients included two with mild yet diffuse coronary artery disease, one with triple-vessel disease, three with double-vessel disease and two with single-vessel disease; the left ventricle was normal in five of the latter eight and hypokinetic in three.

Hence, during follow-up, a total of 14 patients had a coronary event (8%, 0.65%/year); two of the 14 had a fatal event, four had a nonfatal myocardial infarction and eight had typical angina, their angiograms showing coronary disease of various degrees. The median interval between angiography and a coronary event was 9.2 years; only one patient had a coronary event <5 years after the first angiogram.

Medical treatment (Table 1). During follow-up, the number of patients receiving oral nitrates decreased from 123 to 33, those taking beta-blockers from 65 to 21 and those taking digitalis from 30 to 14; in contrast, the number of patients taking calcium channel blockers increased from 43 to 56, those taking diuretics from 17 to 27 and those taking anticoagulant agents or aspirin from 8 to 28. Manifestation of coronary events did not correlate with treatment.

Discussion

The syndrome of anginalike chest pain was reported in 1897 by Osler (21), who called it pseudo-angina pectoris and described it as persistent chest pain that lasted for years and was found more frequently in women. In his experience, it had a favorable prognosis in contrast to that of "true angina." Today, the widespread diagnostic use of coronary angiography allows a closer analysis of this syndrome, especially with regard to prognosis.

Long-term prognosis of patients with anginalike chest pain. This study, with a median follow-up interval of 12.4 years (maximum 15.8) represents the longest-term study of its type to date. It confirms that patients with typical angina or anginalike chest pain and normal coronary angiograms have a favorable prognosis and a low rate of coronary morbidity and mortality, even in the presence of positive exercise test results. There was one fatal acute myocardial infarction (0.05%/year) and an additional sudden death in our study group; thus, the risk of death from coronary artery disease is 0.09%/year, not higher than that in the overall population aged 45 to 65 years (0.9%/year) (20). The rate of nonfatal myocardial infarctions (0.18%/year) was also not different from that of the overall population. Most important, all coronary events occurred in patients with an increased number of risk factors at entrance into the study (2.4/patients with events vs. 1.3/patients without events, $p < 0.01$); that is, in 25% of patients with three risk factors and in 5.5% of those with one risk factor, but in no patient without risk factors.

Furthermore, in our study we found no correlation between the severity of the initial anginalike chest pain (duration, intensity of attacks) and the occurrence of later coronary events (12). This observation again strongly suggests that the

chest pain was not related to an ongoing atherosclerotic process.

Comparison with previous studies (Table 4). Several previous studies (1,3,5,6,8,11,13,16,17) of patients similar to ours reported no coronary events during follow-up; however, these studies had a relatively short follow-up interval (average 29.4 months; range 13 to 76) and a small number of patients (average 61; range 13 to 200); in fact, only four (4,10,14,17) of the 18 studies cited in Table 4 in addition to our own had a follow-up duration >5 years, and only 1 (17) of these long-term studies reported no coronary events. Hence, studies of short duration and a small number of patients should be judged with caution with regard to prognosis. A long follow-up period is mandatory to pass judgment on the course of these patients, as is suggested by the observation that early atherosclerotic changes such as fatty streaks (22,23) and even plaques of considerable size (24,25) can be located entirely in the arterial wall for long periods, not recognized by coronary angiography. Several studies have reported a higher incidence of patients with a coronary event during follow-up (for example, 0.83%/year and 0.97%/year, respectively, in the studies of DeMaria et al. [10] and Inzer et al. [12] vs. 0.65%/year in ours); however, some of these studies (1,6,9,10,12,14) included patients with diameter stenoses up to 30% and 50%, whereas none of our patients had even minimal lesions. That all 14 of our patients with a fatal or nonfatal coronary event experienced the event relatively late (i.e., after an average of 111.1 months [median 9.2 years]), suggests that their chest pain at entrance into the study was probably not related to coronary artery disease.

Pathophysiology. The causes of the syndrome of anginalike chest pain and normal coronary angiographic findings are thought to be functional (coronary artery spasm) (26,27) or anatomic (involving both large [26,27] and small coronary arteries [arterioles] [16,17,27,28]), resulting in an insufficient dilator capacity (29-31). Recent data (28,32-35) suggest that endothelial dysfunction in the coronary vascular area due to impaired endothelium-derived relaxing factor/nitrous oxide production could be a major cause. This form of the disease is usually associated with hypercholesterolemia (28), which was present in only 47 (27%) of our patients. Hence, the clinical syndrome is probably the result of a variety of causes—functional, anatomic and a mixture of both (27,29).

Limitations of the study. Our study has two principal limitations. 1) Our patients were followed up only clinically, not angiographically by repeated angiograms at fixed intervals. This procedure was followed mainly for ethical reasons; angiograms were repeated only on the basis of clear indications such as a change in the pain pattern from atypical to typical angina, often independent of exercise tests, or in the presence of acute myocardial infarction. Hence, it is possible that some of our patients may have had during the follow-up period clinically nonmanifest coronary artery disease, restricted to the vessel wall (fatty streaks, small intramural plaques) or plaques protruding into the vessel lumen, without limiting flow and, therefore, clinically silent (36). Because the follow-up interval

Table 4. Long-Term Follow-Up Studies of Patients With Normal Findings on Coronary Angiograms (modified from Inzer et al. [12])

First Author (ref. no.)	Year	Patients			Average Follow-Up Interval (mo)	No. of Coronary Deaths	Myocardial Infarction	Patients With Repeat Angiography		Chest Pain (%)	
		No.	Average Age (yr)	% Female				Total No.	With CAD	Initial	Follow-Up
Waxler (1)	1971	86*	44	100	15	0	0	0	—	100	100
Bemiller (2)	1973	37	43	43	49	1† (2.7%) [0.66%]	0	7	0	100	100
Kemp (3)	1973	200	47	50	36	0	0	5	0	100	90
Humphries (4)	1974	93	—	—	12-144	0	5‡	0	—	98	52
Day (5)	1976	45	43	50	25	0	0	0	—	100	68
Marchandise (6)	1978	22	49	58	52	0	0	22	0	—	—
		26§	49	31	37	0	2	26	7	—	—
Ockene (7)	1980	57	48	60	16	0	0	0	—	100	70
Pasternak (8)	1980	159*	46	45	43	0	1	0	—	100	74
Proudfit (9)	1980	164§	—	38	120	16¶ (9.7%) [0.97%]	14	21	12§	92	40
		357	—	38	120	2	2	10	4	92	40
DeMaria (10)	1980	97	—	—	32	0	1	0	—	—	—
Gleichmann (11)	1981	15	49	—	13-64	0	0	0	—	100	93
Inzer (12)	1981	121§	49	60	40	3† (2.5%) [0.83%]	4	7	3	—	80
Faxon (13)	1982	72	48	42	24	0	0	0	—	100	76
Kemp (14)	1986	3,136	49	53	84	14# (0.44%) [0.06%]	—	—	—	—	—
		915§	52	45		18 (1.96%) [0.28%]	—	—	—	—	—
Van Dorpe (15)	1987	142	46	42	49	0	1	0	—	86	50
Opherk (16)	1989	40	48	25	48	0	0	6	0	100	100
Pupita (17)	1989	13	49	77	76	0	0	1	0	100	100
Current study	1995	178	48	34	144	2 (1.1%) [0.09%]	5	21	13	176	133

*Inclusion of patients with stenoses $\leq 30\%$. †Sudden death, probably of coronary cause. ‡By the patient's history. §Inclusion of patients with stenoses $\leq 50\%$. ||Impairment of preexisting coronary artery disease (CAD). ¶Assumed in 12 patients, proved in 4. #Cardiac death. ref. = reference; — = no data available. () = percent over entire follow-up period; [] = percent per year.

was rather long, such changes could have developed after entrance into the study and, therefore, initially would not have been related to chest pain.

2) No attempts were made to further analyze the cause of pain by additional techniques, for example by provoking coronary artery spasm with ergonovine. Most probably, the pain experienced by these patients was due to a variety of causes, the common denominator being the persistence of pain and the normal angiographic findings.

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